Exhibit A

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JENNIFER CRYER, PETER KILLE,
ANDREW PAUL MORBY and RICHARD CHARLES BROWN

Appeal 2009-011266
Application 10/111,676
Technology Center 1600

Decided: April 23, 2010

Before ERIC GRIMES, RICHARD M. LEBOVITZ,
and JEFFREY FREDMAN, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on an appeal under 35 U.S.C. § 134 by the Patent Applicants from the Patent Examiner's rejections of claims 1, 2, 4-6, 8-10, 15, and 16. The Board's jurisdiction for this appeal is under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

The claims are directed to methods for the quantification of a chemical, mixture of chemicals, or other external factors. The method involves detecting changes in the level of a transcribed mRNA which is produced in response to the chemical or external factor. The mRNA is detected by a chemiluminescent signal from an oligonucleotide, labeled with acridinium, which is bound to the mRNA.

Claims 1, 2, 4-6, 8-10, 15, and 16 are pending. The claims stand rejected by the Examiner as follows:

1. Claims 1, 2, 8-10, 15, and 16 under 35 U.S.C. § 103(a) as obvious in view of Bao (U.S. Patent No. 6,020,121, Feb. 1, 2000), Arnold '174 (U.S. Patent No. 5,283,174, Feb. 1, 1994), and Nelson (Detection of Acridinium Esters by Chemiluminescence, *Nonisotopic Probing, Blotting, and Sequencing,* pp. 391-428, 1995) (Ans. 4-5).

2. Claim 4 under 35 U.S.C. § 103(a) as obvious in view of Bao, Arnold '174, Nelson, and Mattingly (U.S. Patent No. 5,783,699, Jul. 21, 1998) (Ans. 12-13).

3. Claims 5 and 6 under 35 U.S.C. § 103(a) as obvious in view of Bao, Arnold '174, Nelson, and Arnold '613 (U.S. Patent No. 4,950,613, Aug. 21, 1990) (Ans. 13-14).

4. Claims 1, 2, 8-10, 15, and 16 under 35 U.S.C. § 103(a) as obvious in view of Ghai (U.S. Patent No. 5,955,269, Sep. 21, 1999), Arnold '174, and Nelson (Ans. 14-15).

5. Claim 4 under 35 U.S.C. § 103(a) as obvious in view of Ghai, Arnold '174, Nelson, and Mattingly (Ans. 21).

6. Claims 5 and 6 under 35 U.S.C. § 103(a) as obvious in view of Ghai, Arnold '174, Nelson, and Arnold '613 (Ans. 22-23).

7. Claims 1, 2, 4-6, 8-10, and 15 under 35 U.S.C. § 112, first paragraph, as lacking a written description of the claim limitation "wherein said transcribed mRNA is not amplified prior to the steps of binding, detecting, and correlating" (Ans. 3-4).

Claims 1, 2, and 15 are representative and read as follows:

1. A method for the quantification of a chemical, mixture of chemicals or other external factors comprising:

exposing to said chemical, mixture of chemicals or other external factors an organism, cell or genetic assembly comprising a gene responsive to said chemical, mixture of chemicals or other external factors such that a change occurs in the level of transcribed mRNA as a result of activation or deactivation of said gene;

binding to said transcribed mRNA an oligonucleotide probe complementary to at least a part of said transcribed mRNA and labelled with a chemiluminescent acridinium molecule;

detecting a chemiluminescent signal from said oligonucleotide probe bound to said transcribed mRNA; and

correlating said chemiluminescent signal from said oligonucleotide probe to a quantity of transcribed mRNA produced in response to said chemical, mixture of chemicals or other external factors to which said organism, cell or genetic assembly was exposed, thereby quantifying said chemical, mixture of chemicals or other external factors;

wherein said transcribed mRNA is not amplified prior to the steps of binding, detecting and correlating.

2. A method for the quantification of a chemical, mixture of chemicals or other external factors comprising:

exposing to said chemical, mixture of chemicals or other external factors an organism, cell or genetic assembly comprising a transcription pathway responsive to said chemical, mixture of chemicals or other external factor such that a change occurs in the level of transcribed mRNA as a result of said exposure;

binding to said transcribed mRNA an oligonucleotide probe complementary to at least a part of said transcribed mRNA and labelled with a chemiluminescent acridinium molecule;

detecting a chemiluminescent signal from said oligonucleotide probe bound to said transcribed mRNA; and

correlating said chemiluminescent signal from said oligonucleotide probe to a quantity of transcribed mRNA produced in response to said chemical, mixture of chemicals or other external factors to which said organism, cell or genetic assembly was exposed, thereby quantifying said chemical, mixture of chemicals or other external factors;

wherein said transcribed mRNA is not amplified prior to the steps of binding, detecting, and correlating.

15. A method for the quantification of a chemical, mixture of chemicals or other external factors comprising:

exposing an organism to said chemical, mixture of chemicals or other external factors, said organism having an organ, cell or genetic assembly comprising a gene or transcription pathway responsive to said chemical, mixture of chemicals or other external factors such that a change occurs in the level of transcribed mRNA as a result of activation or deactivation of said gene or transcription pathway;

obtaining from said organism a total RNA preparation containing said transcribed mRNA;

directly binding to said transcribed mRNA in said total RNA preparation an oligonucleotide probe complementary to at least a part of said transcribed mRNA and labelled with a chemiluminescent acridinium molecule;

detecting a chemiluminescent signal from said oligonucleotide probe bound to said transcribed mRNA; and

correlating said chemiluminescent signal from said oligonucleotide probe to a quantity of transcribed mRNA produced in response to said chemical, mixture of chemicals or other external factors to which said organism, cell or genetic assembly was exposed, thereby quantifying said chemical, mixture of chemicals or other external factors;

wherein said transcribed mRNA is not amplified prior to the steps of binding, detecting, and correlating.

BAO AND GHAI OBVIOUSNESS REJECTIONS

Since Appellants argued the rejections as a group (App. Br. 15), we consider all the obviousness rejections together. Claims 4-6, 8-10, and 16 fall with claims 1, 2, and 15 because separate arguments for their patentability were not provided. *See* 37 CFR § 41.37(c)(1)(vii).

Statement of the Issues

The issues in the obviousness rejections are as follows:

1) Whether the cited prior art describes or suggests:

- direct detection of mRNA without need of mRNA amplification or separation; and
- quantifying chemicals or external factors by the claimed "correlating" step.

2) Whether the combination of cited prior art provides the motivation with an expectation of success to have made the claimed method.

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).

> [I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. Sakraida and Anderson's-Black Rock are illustrative—a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Id.

Findings of Fact

Bao

1. Bao describes "screening methods for potential inhibitors of global regulators of bacterial pathogenes." (Bao, col. 6, ll. 10-12.)

2. "In a preferred embodiment, the screening involves detecting the amount of transcriptional or translational product from a hybrid DNA construct inserted in a cell, for cells grown in the presence and absence of the agent." (*Id.* at col. 6, ll. 53-55.)

3. In one example, Bao teaches inhibiting the transcription of RNAIII from the P3 promoter of Staphylococcus aureus with various compounds (*id.* at col. 2, ll. 45-61).

4. Bao's Figure 14 shows Northern Blots. "Total RNA is isolated from treated and untreated cells . . . The RNA is probed on a Northern Blot with a RNAIII-specific probe . . . The Northern Blot shows varying levels of reduction of RNAIII expression caused by the three active compounds." (*Id.* at col. 9, ll. 4-14; *see also* col. 21, ll. 4-33.)

5. Figure 15 shows "[q]uantitation of Northern Blot from FIG. 14. Probes were labeled in a manner that allowed chemiluminescent detection." (*Id.* at col. 9, ll. 23-24; *see also* col. 21, ll. 4-33.)

6. Bao describes testing compounds ("hits") (*id.* at col. 28, ll. 54-55) for their ability to inhibit RNAIII transcription. "Overall, 15 of the 16 hits tested caused a quantitative decrease in production of RNAIII, as assayed by Northern Blot" (*id.* at col. 29, ll. 5-7).

7. An amplification step is not utilized in the screening and RNA detection methods of Bao summarized in Findings of Fact 3-6.

Arnold '174

8. Arnold '174 describes using chemiluminescent acridinium ester labeled oligonucleotide probes in a hybridization assay format for detecting the presence of target polynucleotide sequences (Arnold '174, Abstract; col. 9, ll. 25-28).

9. Arnold '174 teaches that its probe system "is useful in probe diagnostics, including infection and genetic and viral disease detection and cancer diagnosis." (*Id.* at col. 5, ll. 34-37.)

10. A hybridization assay was exemplified in Arnold '174 in which a probe for a target C. trachomatis rRNA was hybridized in solution with C. trachomatis rRNA (*id.* at col. 15, ll. 30-49).

11. Detection of a chimeric mRNA associated with chronic myelogenous leukemia (CML) was also described by Arnold '174 (*id.* at col. 25, l. 50 to col. 26, l. 46).

Nelson

12. Nelson describes oligonucleotide probes labeled with chemiluminescent acridinium esters (Nelson, p. 393-394).

13. A hybridization protection assay (HPA) is described involving hybridization, differential hydrolysis of the chemiluminescent acridinium esters ("AE"), and detection. (*Id.* at 398.)

14. A hybridization assay is described in which "AE-probe is added to a solution containing the target nucleic acid, and the mixture is incubated." (*Id.* at 396.)

15. According to Nelson, there "are several advantages to using the chemiluminescent AE as a detection label, including high inherent

sensitivity, low quenching, simplicity, ease of handling and disposal, precise chemical control, and a long shelf-life. Furthermore, these properties are not adversely affected by attachment of the AE to oligonucleotide probes, nor are the hybridization characteristics of the oligonucleotide probe compromised." (*Id.* at 399.)

16. Nelson also describes the advantages of its assay format, including the "in-solution approach" and the ability to detect both DNA and RNA targets (*id.* at 400).

17. Nelson states that "AE-probes cannot be run under standard polyacrylamide gel electrophoresis conditions (although other types of conditions of electrophoresis are feasible)." (*Id.* at 401.)

18. Nelson states that the "AE-probe method can be used for the in-solution detection of virtually any target nucleic acid, provided the target possesses a hybridizable probe region . . . and is available in sufficient quantity to be within the sensitivity range of the assay." (*Id.*)

Ghai

19. Ghai describes methods of "screening foods and food substances which are capable of modulating the expression of one or more genes that are related to or associated with disease or undesirable condition" (Ghai, at col. 3, ll. 40-45).

20. Ghai teaches that its methods are related to down- and up-regulating gene expression using cell-based assays (*id.* at col. 3, l. 54 to col. 4, l. 12).

21. The gene expression "can be assessed directly by detecting and/or measuring the level of messenger RNA of the disease-related gene" (*id.* at

col. 17, ll. 44-46). One disclosed method involves labeled nucleic acid probes to detect the nucleic acid (*id.* at col. 18, ll. 15-24).

22. "Expression of the disease-related gene may be achieved by assaying, in a cell lysate, the level of messenger RNA of the disease-related gene (e.g., by Northern blot analysis)" (*id.* at col. 4, ll. 20-22).

23. In one embodiment of the invention, processed foods containing an increased level of a nutraceutical for consumption by a subject can be prepared by (1) contacting a food or food substance with test cells containing a disease-related gene or portion thereof for an interval sufficient for a nutraceutical to modulate the expression of the disease-related gene or portion thereof; (2) measuring the expression of the disease-related gene; (3) comparing the level of expression with that of a control cell which was not contacted with the nutraceutical; and (4) adding an appropriate amount of the nutraceutical in the processed food.

(*Id.* at col. 27, ll. 4-18.)

24. Ghai describes hybridization assays involving Northern blot analysis, dot blot, and slot blot hybridization (*id.* at col. 18, ll. 12-13).

25. Ghai describes an example of a nutraceutical that regulates expression of the human lysyl oxidase (LOX) gene. Using a reporter gene construct (CAT), Ghai reports:

> Epigallocatechin gallate [a food substance found in tea] also showed a concentration dependent effect producing a 4.45 and 4.7 fold increase in promoter activity at 100 and 200 µg/ml respectively. Some of the compounds, such as kojic acid were toxic when added to the cultured cells even though the presence of 10 µg/ml kojic acid raised the promoter activity by 2.3 fold.

(*Id.* at col. 30, ll. 45-56.)

26. An amplification step is not utilized in the screening and RNA detection methods of Ghai summarized in Findings of Fact 24.

ANALYSIS

Indirect methods

Appellants contend that Bao and Ghai teach only "indirect methods" comprising "separating rRNA or mRNA from total RNA such as by gel electrophoresis," while "the present disclosure sets forth methods for direct detection of mRNA . . . without any need for amplification of mRNA or even separation therefrom from total RNA." (App. Br. 16.)

Both Bao and Ghai explicitly disclose methods in which transcribed RNA is detected without an amplifying step (FF7 & 26), as required by independent claims 1, 2, and 15 is this appeal. Thus, even if it is true that Ghai discloses amplification in certain of its methods (App. Br. 18), there is express description in Ghai of methods which do not require it.

Appellants attempt to distinguish the claimed method from Bao and Ghai on the basis of "indirect methods," i.e., methods which involve hybridizing the oligonucleotide probe labeled with chemiluminescent acridinium to mRNA in a total RNA preparation, without performing a separation step. As correctly concluded by the Examiner, claims 1 and 2 do not exclude separating the mRNA prior to oligonucleotide binding, but rather recite "binding to said transcribed mRNA an oligonucleotide probe" and thus encompass separation steps. For this reason, Appellants' argument concerning "indirect methods" does not distinguish over claims 1 or 2.

Claim 15, however, recites "directly binding to said transcribed mRNA in said total RNA preparation an oligonucleotide probe." We interpret this phrase to mean that the labeled probe is hybridized ("binding") to the target mRNA when it is present in the total RNA pool. That is, persons of ordinary skill in the art would interpret claim 15 to exclude an

RNA separation step, such as the Northern blot utilized in certain embodiments of Bao and Ghai. Nonetheless, we conclude that the Examiner correctly determined that such step is described and suggested by the cited prior art.

First, as noted by the Examiner, Ghai's disclosure is not limited to Northern blot separation technology to detect probe binding. Ghai discloses Northern blotting as an example of a detection method for analyzing levels of RNA (FF22, "e.g.,"), but also mentions slot and dot blots in hybridization assays (FF24). Appellants have therefore read Ghai's disclosure too narrowly.

Secondly, also as found by the Examiner, Bao exemplifies Northern blot analysis, but does not state that its methods could not be used, or would be inoperable, with other RNA detection methods.

Finally, and independently, the Examiner's rejection is not based on Bao or Ghai alone, but was grounded on additional references. Arnold '174 describes using the claimed chemiluminescent acridinium ester labeled oligonucleotide probe in a hybridization assay performed in solution without separating the target rRNA from the total rRNA (FF8-10). Nelson also described a method of detecting binding of the acridinium labeled oligonucleotide probe in solution (FF14), touted advantages of the "in-solution" assay (FF15), and reported that that the method "can be used for the in-solution detection of virtually any target nucleic acid" (FF18). Therefore, such methods would have reasonably suggested utilizing a direct approach in either Bao or Ghai.

In sum, we find that "direct" limitation (i.e., detection of mRNA in a total RNA preparation) recited in claim 15 is disclosed or reasonably

suggested by Bao or Ghai combined with Arnold '174 and Nelson as determined by the Examiner.

Quantifying step

Appellants contend that "[n]owhere does Ghai teach quantifying the amount of such compounds in food based on direct detection of gene expression or downregulation as in the present invention, further without amplification of the transcribed mRNA or separation of transcribed mRNA from total RNA." (App. Br. 18.) Appellant argues that the ratio in Ghai which the Examiner characterized as "quantification" is "still essentially an indicator that the nutraceutical is present in the food or it is not, and provides no element of true quantification as does the present Appellant's method." (*Id.*)

Claims 1, 2, and 15 recite "correlating said chemiluminescent signal from said oligonucleotide probe to a quantity of transcribed mRNA produced in response to said chemical, mixture of chemicals or other external factors . . . , thereby quantifying said chemical, mixture of chemicals or other external factors." We interpret "correlating" to mean that a relationship is established between the signal and the quantity of transcribed mRNA. We further interpret the following "thereby" clause to state the result of the "correlating" step, and not to further limit the claim. In other words, "quantifying" as recited in the "thereby" clause is a consequence of establishing a relationship between a signal from the probe to the "quantity of transcribed mRNA." This step is described and suggested by the cited prior art.

Ghai describes measuring levels of messenger RNA produced in response to a nutraceutical agent (FF21-FF23). One example involves using labeled probes (FF21). Thus, Ghai would use the signal from the labeled probe to determine the "level" or quantity of mRNA, and thus satisfies the correlating step recited in claims 1, 2, and 15 because it establishes a quantitative relationship between the probe signal and the RNA quantity.

Furthermore, Ghai reasonably suggests determining effective quantities of the nutraceutical based on RNA expression levels. Ghai teaches measuring the level of a disease-related gene's expression and then "adding an appropriate amount of the nutraceutical in the processed food." (FF23.) Persons of ordinary skill in the art would infer from these steps that to add an appropriate amount of the nutraceutical, the amount of nutraceutical needed to modulate the expression of the disease-related gene would be determined by establishing a relationship between the quantity of nutraceutical, probe signal, and levels of RNA.

No motivation and lack of reasonable expectation of success based on Nelson's disclosure

Nelson writes: "AE-probes cannot be run under standard polyacrylamide gel electrophoresis conditions (although other types or conditions of electrophoresis are feasible)." (FF 17.)

Appellants contend that Nelson's teaching, as quoted above, would have deterred the ordinary skilled worker from "modifying the procedures set forth by Bao and Ghai to include the probes of Arnold and Nelson." (App. Br. 21.) They argue:

> Nelson himself, one of the two inventors of a secondary reference relied on by the Examiner (Arnold I), *in a reference that published one year after the issue date of the Arnold I patent*, expressly negates use of the described HPA assay and acridinium-labeled probe in an electrophoretic assay for detection of mRNA.

(*Id.*)

The Examiner relied on Arnold '174 and Nelson for describing the use of an acridinium-labeled oligonucleotide probe in a solution hybridization assay that does not require electrophoresis. In other words, the assays described in Arnold '174 and Nelson would be *substituted* for those of Bao and Ghai. Nelson explicitly described the advantages of its probes and assay (FF15-16) and its broad applicability (FF18), providing reason for one of ordinary skill in the art to have utilized Nelson's method instead of Northern blot analysis. "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 416.

Nelson states that its acridinium probes "cannot be run under standard polyacrylamide gel electrophoresis conditions." (FF17). However, even were Bao and Ghai's assays utilized, the probes would not be "run" on the gel – rather the probes would be hybridized to the paper onto which the RNA from the acrylamide had been transferred – as is the case for a Northern blot. Nonetheless, Nelson's statement merely acknowledges a shortcoming with "standard polyacrylamide gel electrophoresis," not all electrophoretic techniques, and certainly not its own in-solution methods.

In sum, Appellants have not established a lack of motivation or expectation of success in combining Bao or Ghai with Arnold and Nelson to have made the claimed invention.

WRITTEN DESCRIPTION REJECTION

Statement of the issue

Claims 1, 2, and 15 recite the negative limitation that the transcribed mRNA produced in response to the chemical or other external factor "is not amplified prior to" the claimed "steps of binding, detecting, and correlating." The limitation was not recited in the original claims when the application was filed, but was added by amendment during prosecution. The Examiner contends that the limitation was not described in the Specification and therefore is "new matter" (Ans. 3). The Examiner reasoned that there was no basis in the Specification to exclude an amplification step and that methods were not originally "contemplate[d] ... which included or specifically excluded performing an amplification step prior to binding, detecting or correlating" (*id.* at 4.)

"[A]n examiner can make out a prima facie case of lack of adequate written description, thus shifting the burden of production to the applicant, simply by identifying specific claim limitations and stating that despite reviewing the specification, he could not find support for those limitations." *Hyatt v. Doll*, 576 F.3d 1246, 1274 (Fed. Cir. 2009). Therefore, the issue in this appeal is whether Appellants rebutted the Examiner's determination that the claims contain subject matter which was not described in the Specification.

Principles of law

To satisfy the written description requirement, the inventor "must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). In describing the claimed invention, there is no requirement that the wording be identical to that used in the specification as long as there is sufficient disclosure to show one of skill in the art that the inventor "invented what is claimed." *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000). Thus, so long as a person "of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996).

Findings of Fact

27. Example 8 describes adding mercury to transformed bacteria and then measuring RNA levels using a hybridization protection assay (Spec. 32-36; *see also* App. Br. 13-14).

28. Example 8 performs its RNA detection without an amplification step.

29. The Specification discloses "existing techniques for analysing mRNA levels such as Northern blotting, RNase protection assays and RT-PCR [reverse transcriptase polymerase chain reaction]," the latter of which persons of ordinary skill in the art would have recognized as an amplification method (Spec. 7: 2-4).

Analysis

While the phrase "wherein said transcribed mRNA is not amplified prior to the steps of binding, detecting, and correlating" as recited in claims 1, 2, and 15 is not literally recited in the Specification, Example 8 describes an example of performing the recited steps in the absence of mRNA amplification. RT-PCR, an amplification method, was recognized as an "existing technique[ ]" for analyzing mRNA levels, but was not utilized in Example 8. In view of these disclosures, persons of ordinary skill in the art would have recognized that amplification could be excluded from the disclosed method. The Specification therefore shows that the inventors "invented what is claimed." *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d at 997. The written description rejection is reversed.

SUMMARY

The obviousness rejections of claims 1, 2, 4-6, 8-10, 15, and 16 are affirmed. The written description rejection of claims 1, 2, 4-6, 8-10, and 15 is reversed.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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